32. (NEW) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the nucleotide sequence of claim 5 or a peptide encoded by said nucleotide sequence, further comprising a purified antibody or an active portion of said antibody that specifically binds a polypeptide encoded by said nucleotide sequence.

REMARKS

Amendments were made to correct informalities and to more clearly claim the invention. No new matter is added herewith. Changes to the application can be seen on a separate page entitled VERSION WITH MARKINGS TO SHOW CHANGES MADE following the signature page. Deletions are in **[bold and brackets]** and insertions are underlined.

Abstract

The Examiner indicates that the amendments to the Abstract filed February 11, 2002 were acknowledged, but an attached abstract was not found. Applicants enclose herewith an abstract on a separate page as required by the Examiner.

Objection to Specification

The Examiner has objected to the specification for containing typographical errors at page 18, line 30, and page 20, lines 23-27. These errors have been corrected by amendment. Applicants respectfully request withdrawal of the objections.

Claim Rejections Under 35 U.S.C. § 112, first paragraph

Claims 5, 14, and 16 were rejected under 35 U.S.C. § 112, first paragraph, for not enabling one of skill in the art to make and use the invention commensurate in scope with the claims. The Examiner notes that the specification enables two human polynucleotides consisting of SEQ ID NO: 1 and 10, a rat polynucleotide of SEQ ID NO: 3 and a mouse polynucleotide of SEQ ID NO: 5 that encodes peroxisomal-associated polypeptide corresponding to SEQ ID NOS: 2, 4, and 6, respectively, and polynucleotide probes of SEQ ID NOS: 7-9 and 11-16. The Examiner asserts that the specification does not enable any pharmaceutical composition comprising a pharmaceutical acceptable carrier and any polynucleotide mentioned above or its

complementary strand and a cell transformed by any vector comprising any partial or total genomic deletion of SEQ ID NO:1 or and homolog thereof.

Claim 5 has been amended to recite an isolated or purified polynucleotide consisting essentially of SEQ ID NO: 1 or its complementary strand, which is clearly enabled by the specification and is stated on record by the Examiner. Claim 14 has been amended to recite a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the nucleotide sequence of Claim 5 or a polypeptide encoded by the nucleotide sequence of Claim 5.

As submitted in the Office Action response filed November 6, 2001, the inventors have demonstrated that the systemic administration of recombinant peroxiredoxin 5 (PRDX5) to mice induced a dose-dependent neuroprotection against excitotoxic brain lesions. Applicants have shown the neuroprotective effects of recombinant PRDX5 administered against neonatal exitotoxic challenge.

Applicants amplified human PRDX5 cDNA by PCR. The PCR product was digested and further ligated into the pQE-30 expression vector. The resulting vector was used to transform *E. coli* strain M15 (pRep4). The bacteria were grown, and pelleted cells were lysed by sonication and clarified by centrifugation. The supernatent containing the recombinant PRDRX5 was loaded on a Ni2+NTA column and eluted. The eluted protein was then dialysed against PBS (pH 7.2).

Excitotoxic brain lesions were induced by intracerebral injection of ibotenate (acting on NMDA and metabotrobic receptors) into developing muse brains of postnatal day 5 mouse pups. Pups were killed five days later and brains were processed for histology, allowing for determination of the size of the neocortical plate (mimicking lesions of full-term human infants) and perventricular cystic white matter lesions (mimicking PVL). Recombinant PRDX5 (0.1-20 mg/kg) was administered by interperitoneal injection immediately after the excitotoxic injections. Effects of PRDX5 were compared to those immediately after the excitotoxic injection. Effects of PRDX5 were compared to those obtained with reference antioxidants including N-acetylcysteine (0.25-250 mg/kg) or catalase-polyethyleneglycol (catalase-PEG; 6,000-600,000 U/kg). Controls received intraperitoneal PBS alone. *In vitro*, neocortical neurons were exposed to 300microM NMDA in the absence or presence of 0.1-100 microM PRDX5 alone or 10 microM PRDX5 with 10 microM dithiothreitol (DTT, a classical electron donor). Apoptotic nuclei were counted following chromatin staining with Hoechst 33258.

Systemically adminstered PRDX5 induced a dose-dependent neuroprotection of the ibotneate-induced lesions of both the cortical plate and the white matter (reduction of up to 63% of the lesion size). N-acetylcysteine and catalase-PEG mimicked PRDX5 effects on excitotoxic lesions. *In vitro*, PRDX5 and DTT displayed a synergetic neuroprotective effect on NMDA-induced neuronal death. This shows that antioxidant drugs, such as PRDX5, are neuroprotective in these models and can be used as a neuroprotective agent in other neurodegenerative conditions associated with oxidative stress. Applicants have demonstrated use of a pharmaceutical composition according to claim 14. Furthermore, Applicants have demonstrated transformation of *E. coli* with a vector according to claim 16.

Applicants also submit a copy of a paper entitled "Overexpression of human peroxiredoxin 5 in Chinese Hamster Ovary cells: effects on cell survival and DNA damage during acute oxidative stress induced by peroxides". This paper demonstrates that overexpression of PRDX5 in host cells decreases damage induced by peroxides. Chinese hamster ovary cells overexpressing human PRDX5 in the cytosol, in mitochondria, or in the nucleus were established by stable transfection. Cells overexpressing PRDX5 were exposed to acute oxidative stress with hydrogen peroxide (20-40 nM) or tert-butylhydroperoxide (20-70 nM) for an hour and viability was evaluated by lactate dehydrogenase assay.

Overexpressing PRDX5 in either cytosolic or mitochondrial compartments significantly reduced cell death with a more effective protection with overexpression of PRDX5 in mitochondria confirming that this organelle is a main target for peroxides. Moreover, DNA damage induced by a sub-lethal concentration of hydrogen peroxide (2-5 mM) or tert-butylhydroperoxide (5-10 mM) was evaluated with the cornet assay.

Overexpression of PRDX5 in the nucleus significantly decreased DNA damage induced by both peroxides. Taken together these results show that overexpression of PRDX5 by Chinese hamster ovary cells in cytosolic and mitochondrial compartments increases cell survival of cells challenged by peroxides and that overexpression of PRDX5 in the nucleus decreases DNA damage induced by peroxides. Applicants have shown that Chinese hamster ovary cells are stably transfected with a vector comprising the cDNA sequence of PRDX5.

Applicants assert that the presently claimed invention is enabled and that the specification provides sufficient support for a pharmaceutical composition consisting essentially of a pharmaceutical acceptable carrier and SEQ ID NO:1 or its complementary strand and a cell

transformed by a vector comprising SEQ ID NO:1 or its complementary strand. Applicants respectfully request withdrawal of the rejection on this basis.

Claims 5, 14, and 16 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to convey to one skilled in the art that the inventor was in possession of the invention at the time of filing. The Examiner asserts that the specification does not provide a written description for a cell transformed by any vector comprising any partial or total genomic deletion of SEQ ID NO: 1 or any homolog thereof and any pharmaceutical composition for treating any disease.

Claim 5 has been amended to recite an isolated or purified polynucleotide consisting essentially of SEQ ID NO: 1 or its complementary strand, which is clearly enabled by the specification and is stated on record by the Examiner. Claim 14 has been amended to recite a pharmaceutical composition comprising a pharmaceutically acceptable carrier and the nucleotide sequence of Claim 5 or a polypeptide encoded by the nucleotide sequence of Claim 5. The Examiner has stated that the specification enables two human polynucleotides consisting of SEQ ID NO: 1 and 10, a rat polynucleotide of SEQ ID NO: 3 and a mouse polynucleotide of SEQ ID NO: 5 that encodes peroxisomal-associated polypeptide corresponding to SEQ ID NOS: 2, 4, and 6, respectively, and polynucleotide probes of SEQ ID NOS: 7-9 and 11-16.

Applicants assert that the presently claimed invention is disclosed in the application as filed. Applicants have clearly shown that they were in possession of an isolated or purified polynucleotide consisting essentially of SEQ ID NO: 1 or its complementary strand, as well as pharmaceutical composition and vectors comprising an isolated or purified polynucleotide consisting essentially of SEQ ID NO: 1 or its complementary strand. Applicants respectfully request withdrawal of the rejection on this basis.

Claim Rejection Under 35 U.S.C. § 102

Claims 5, 9, 12, 14, and 16 were rejected under 35 U.S.C. § 102(e) as being anticipated by US Patent No. 6,197,543 (herein after referred to as "'543 patent"). 35 U.S.C. § 102(e) states, *inter alia*, that a person shall be entitled to a patent unless the invention was described in a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent. Applicants note that the present application claims priority

to Belgian application 9700692 (a copy of which is filed herewith), filed August 20, 1997, which predates the filing date of the '543 patent that was filed on October 28, 1997.

Furthermore, Applicants have amended the claims to remove the term "comprising" and have replaced it with "consisting essentially of". The '543 patent does not disclose an isolated or purified polynucleotide consisting essentially of SEQ ID NO: 1 or its complementary strand. Applicants respectfully request withdrawal of the rejection on this basis.

Claim Rejection under 35 U.S.C. § 103(a)

Claims 9 and 16 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Hillier et al. (Accession No. W00593) or Hillier et al. (Accession No. N91311) or Hillier et al. (Accession No. W38597) or Hillier et al. (Accession No. N68467) or Hillier et al. (Accession No. N42215) or Hillier et al. (Accession No. H20154) or Marra et al. (Accession No. W71344), each in view of Sambrook et al. Claim 9 recites a vector comprising the polynucleotide of claim 5, namely an isolated or purified polynucleotide consisting essentially of SEQ ID NO: 1 or its complementary strand. Amended Claim 16 recites a cell transformed by the vector according to claim 9. Applicants have enclosed herewith a paper, referred to above, in which Chinese hamster ovary cells were stably transformed with a vector comprising the nucleotide sequence of PRDX5. The plasmid pEF-BOS was used as a mammalian expression vector. The vectors produced could distinctly induce the overexpression of the PRDX5 in different subcellular compartments in the cytosol, in mitochondria, or in the nucleus. Overexpressing PRDX5 could surprisingly and significantly reduce cell death during acute oxidative stress.

Cells transfected with the vector were, surprisingly, protected against acute oxidative stress. Furthermore the survival of these cells when challenged by peroxides was increased when compared to non-transfected cells. Applicants assert that these unexpected results could not have been deduced from the references cited by the Examiner. One of skill in the art would not have a reasonable expectation of success if they were to combine any of the references cited in order to make or use the presently claimed invention. Applicants respectfully request withdrawal of the rejection on this basis.

Conclusion

Applicants assert that the present application is in condition for allowance. Should any issues arise which may delay prosecution of the present application the Examiner is respectfully invited to contact the under-signed attorney at the telephone number below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: Dec. 18, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Deletions are in **[bold and brackets]** and insertions are underlined.

IN THE ABSTRACT:

Please insert the Abstract attached hereto as page 24 of the application as filed.

IN THE SPECIFICATION:

Please amend the paragraph beginning on page 18, line 27, as follows:

As represented in the enclosed Figure 4, the Inventors have identified upon the genomic DNA (SEQ ID NO: 10) 5 exons and 5 introns. By RT-PCR (using primers 5'-gggtatgggactagctggcg-3' and 5'-ctggccaacattccaattgcag-3') and according to the genomic sequence, 4 different cDNAs corresponding to the transcription of the said genomic DNA have been identified in human lung and in human brain. A first cDNA of 736 bp corresponds to the cDNA encoding the complete amino acid sequence of the B18 protein according to the invention. However, 3 other cDNAs of 601, 604, and 469 bp were also identified, and comprise specific splicings of one of more exons.

Please amend page 20, line 25 as follows:

- high bone mass syndrome (MIM **[n°]**No. 601884),

IN THE CLAIMS:

Please amend the following claims:

5. (FOUR TIMES AMENDED) An isolated or purified polynucleotide **[comprising]** consisting essentially of SEQ ID NO: 1 or its complementary strand.

14. (FOUR TIMES AMENDED) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the nucleotide sequence of claim 5 or a peptide encoded by said nucleotide sequence.

16. (TWICE AMENDED) A cell transformed by the vector according to claim 9 **[or comprising a partial or total genomic deletion of SEQ ID NO:1]**.

Please add the following claims:

28. (NEW) A purified antibody or an active portion of said antibody that specifically binds a polypeptide encoded by the nucleotide sequence of claim 5.

29. (NEW) A diagnostic device comprising a polypeptide encoded by the nucleotide sequence of claim 5.

30. (NEW) A diagnostic device comprising an antibody according to claim 28.

31. (NEW) The purified antibody of claim 28, wherein said antibody is a monoclonal antibody.

32. (NEW) A pharmaceutical composition comprising a pharmaceutically acceptable carrier and the nucleotide sequence of claim 5 or a peptide encoded by said nucleotide sequence, further comprising a purified antibody or an active portion of said antibody that specifically binds a polypeptide encoded by said nucleotide sequence.